DOSAGE REGIMEN OF AN S1P RECEPTOR MODULATOR

The present invention relates to a dosage regimen of an S1P receptor modulator or agonist in the course of the treatment of patients suffering from an inflammatory or autoimmune disease or disorder, for example multiple sclerosis (MS).

Multiple sclerosis is the chief cause of neurological disability in young adults and the most common demyelinating disorder of the central nervous system. Available therapies such as interferon-β and glatiramer acetate have modest efficacy and marginal effects on the progression of disability. These biological agents are administered parenterally and are associated, e.g., with injection site reactions and pyretic symptoms, such as flu-like symptoms. Therefore, there is a strong medical need for a safe and effective oral treatment of multiple sclerosis.

Of those people with multiple sclerosis who receive treatment, a significant number continue to experience disease activity clinically or experience side effects that include flu-like symptoms. Immediate post-injection reactions and injection site reactions. As a result, a substantial population of patients are untreated. Including many with active disease. These MS patients have either tried an existing therapy but discontinued due to intolerance, adverse effects, or perceived lack of efficacy or have not started any therapy because of their concern with adverse effects, fear of self-injection, fear of needles, or belief that currently available options are not effective enough to warrant trial. Thus, there is a significant unmet need for effective new therapies in MS, which limit or reduce the possible adverse events or side effects.

S1P receptor modulators are compounds which signal as agonists at one or more sphingosine1-phosphate receptors, e.g. S1P1 to S1P5. Agonist binding to a S1P receptor may e.g. result in dissociation of intracellular heterotrimeric G-proteins into Gα-GTP and Gβγ-GTP, and/or increased phosphorylation of the agonist-occupied receptor and activation of downstream signaling pathway kinases.

S1P receptor modulators are valuable compounds for the manufacture of medication for the treatment of various conditions in mammals, especially in human beings. For example, efficacy in transplantation has been demonstrated in rats (skin, heart, liver, small bowel), dogs (kidney), and monkeys (kidney) models. Due to their immune-modulating potency, S1P receptor modulators are also useful for the treatment of inflammatory and autoimmune diseases. Treating such diseases usually requires prolonged taking of medication, and maintaining the adequate drug regimen over time.

Oral fingolimod is the first compound in the new class of therapeutics called sphingosine 1-phosphate receptor modulators. Fingolimod is believed to reduce the number of lymphocytes circulating in the blood stream by reversibly trapping a proportion of them in the lymph nodes. Consequently, the number of activated lymphocytes reaching the brain is decreased, resulting in reduced inflammatory destruction. This is a new mechanism of action for MS.

FTY720 efficacy in the treatment of multiple sclerosis has been shown in humans (e.g. as described in "FTY720 therapy exerts differential effects on T call subsets in multiple sclerosis". Mehling M, et al., Neurology. 2008 Oct. 14; 71(16):1281-7; and "Oral fingolimod (FTY720) for relapsing multiple slerosls". Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman C H, Haas T, Kom A A, Karisson G, Radue E W; FTY720 D2201 Study Group. N Engl J Med. 2006 Sep. 14; 355(11):1124-40.).

Administration of a S1P receptor modulator, such as fingolimod may induce adverse events, such as a transient reduction of the heart rate and cardiac conduction at treatment initiation. In particular it has been described that administration of 1.25 mg of FTY720 may induce a decrease in heart rate of approximately 8 beets/min ("FTY720: Placebo-Controlled Study of the Effect on Cardiac Rate and Rhythm in Healthy Patients", Robert Schmouder, Denise Serra, Yibin Wang, John M. Kovarik, John DiMarco, Thomas L. Hunt and Marie-Claude Bastien. J. Clin. Pharmacol. 2006; 46; 895.).

Because of such a possible adverse event, administration of the compound to the patients may have to be made under full and constant medical control, in order to check that the cardiac rhythm is maintained at an acceptable level and no high degree atrioventricular block occurs. Patients may have to stay in hospitals which complicate the treatment and increase the costs of treatment occurrence of adverse events during a drug treatment may induce patient hospitalization or prolongation of existing hospitalization.

Such possible events may also cause the patients to interrupt their treatment, change the recommended dosing regimen on their own or take the medication on an irregular basis, without any medical support or recommendation for doing that. While it is paramount for treating inflammatory or autoimmune diseases, such as for example multiple sclerosis, that the adequate medication is taken over a long period of time, sometimes during the whole life of the patient, and the adequate drug regimen is kept over such a long period of time.

Therefore there is a need to reduce or manage the possible adverse events which may be generated by administration of such a S1P receptor modulator, while administering a dosage which is adequate to treat or prevent the disease for which the compound is administered during the required period of treatment.

More specifically, there is a need to provide an efficient treatment for treating an inflammatory or autoimmune disease or disorder, such as multiple sclerosis, for a large population of multiple sclerosis patients, including patients who could be more exposed or more sensitive to said possible adverse events, patients who were never treated or diagnosed for an inflammatory or autoimmune disease or disorder

There is furthermore a need to ameliorate patient compliance.

BRIEF DISCLOSURE OF THE INVENTION

Surprisingly it has been found that by administering a S1P receptor modulator or agonist, such as fingolimod, according to the specific dosage regimen or method of treatment of the invention, it is possible to treat the patient efficiently while controlling, reducing or abolishing the possible adverse events, e.g. side effects, which may be associated with administration of such a compound.

A further benefit is that the dosing regimen and methods of treatment of the invention permit to administer a S1P receptor modulator or agonist, such as fingolimod, to patients who otherwise may have been reluctant or not could not have been instructed to take that medication. In particular they permit to treat patients suffering from an inflammatory or autoimmune disease or disorder, such as multiple sclerosis, for which the ratio risk/benefit may otherwise be less favourable. Such patients are for example patients